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Case Report

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A Case of Hemophagocytic Lymphohistiocytosis following Second Dose of COVID-19 Vaccination

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Keywords
Hemophagocytic lymphohistiocytosis · COVID-19 · Pandemic · SARS-CoV-2 vaccine

Abstract
Hemophagocytic lymphohistiocytosis (HLH) is a rare, severe hyperinflammatory disease characterized by overproduction of cytokines and hemophagocytosis of hematopoietic cells, resulting in multiorgan failure. Prompt treatment initiation is essential for patient survival. The coronavirus disease 2019 (COVID-19) pandemic has led to the rapid development of several vaccines, including BNT162b2 by Pfizer-BioNTech. Few cases of immune-mediated complications of COVID-19 and its vaccines have been reported, characterized by persistent stimulation of the immune system, resembling HLH. We report the case of a 21-year-old man with secondary HLH following a second dose of the BNT162b2 vaccine. The patient did not have primary HLH or other contributors to secondary HLH and met the HLH-2004 diagnostic criteria. He was safely treated with steroid pulse therapy alone, without etoposide, cyclosporin, or immunoglobulins, which are recommended for pediatric patients. Physicians need to be aware of such severe complications following a second dose of the COVID-19 vaccine.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to the rapid production of several vaccines [1]. Currently, there are two messenger RNA (mRNA)-based vaccines (BNT162b2 by Pfizer-BioNTech and mRNA-1273 by Moderna Therapeutics) and two DNA vaccines utilizing adenovirus vectors (ChAdOx1 nCov-19 by AstraZeneca-Oxford and Ad26.COV2.S by Janssen-Johnson & Johnson). Although there was a significant decrease in COVID-19-associated mortality, various adverse events have been described after vaccination [2]. Most were in the form of mild localized or systemic symptoms such as injection site pain, fever, myalgia, headache, or fatigue which subsided spontaneously with conservative care only [3]. However, rare but fatal adverse events, including thrombotic thrombocytopenia and myocarditis, were also reported, and as the number of vaccinated people increased, its frequency increased [4, 5]. Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening, hyperferritinemic, hyperinflammatory syndrome, and HLH as a complication of COVID-19 vaccination has rarely been reported, regardless of vaccine type; all but one case occurred at the first dose [6–14]. Herein, we report a case of HLH following the second dose of BNT162b2 vaccination.

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Table 1. Diagnostic criteria of HLH and laboratory results of a 21-year-old man

Diagnostic criteria[a]	At diagnosis	Day 26
Molecular diagnosis consistent with HLH	Not evaluated	–
Diagnostic criteria for HLH fulfilled (≥5 of 8 criteria)	8 of 8	
Fever	39.5°C	36.4°C
Splenomegaly	Yes	–
Cytopenias (affecting ≥2 of 3 lineages)	2 lineages	
Hemoglobin <90 g/dL	9.6	13.6
Platelets $<100 \times 10^9$/L	37	205
Neutrophils $<1.00 \times 10^9$/L	0.35	4.20
Fasting hypertriglyceridemia and/or hypofibrinogenemia		
Fasting triglycerides ≥3.0 mmol/L	32.4	4.4
Fibrinogen ≤1.5 g/L	1.3	1.62
Hemophagocytosis in BM	Yes	–
Low or no NK cell activity	Yes	–
Ferritin ≥500 µg/L	23,639	204
Soluble CD25 ≥2,400 U/mL	5,776	–
Other laboratory results (reference range)		
Aspartate aminotransferase (normal range, 0–40), U/L	292	24
Alanine aminotransferase (normal range, 0–40), U/L	359	45
Total bilirubin (normal range, 0–1.20), mg/dL	10.27	1.12
Direct bilirubin (normal range, 0.13–0.47), mg/dL	9.59	0.91
Lactate dehydrogenase (normal range, 0–250), U/L	881	217
Albumin (normal range, 3.5–5.2), g/dL	3.0	4.8
Urea nitrogen (normal range, 6.0–20.0), mg/dL	19.4	17.6
Creatinine (normal range, 0.70–1.20), mg/dL	0.80	0.81
C-reactive protein (normal range, 0–0.5), mg/dL	1.3	<0.03

HLH, hemophagocytic lymphohistiocytosis. [a] HLH-2004 diagnostic criteria.

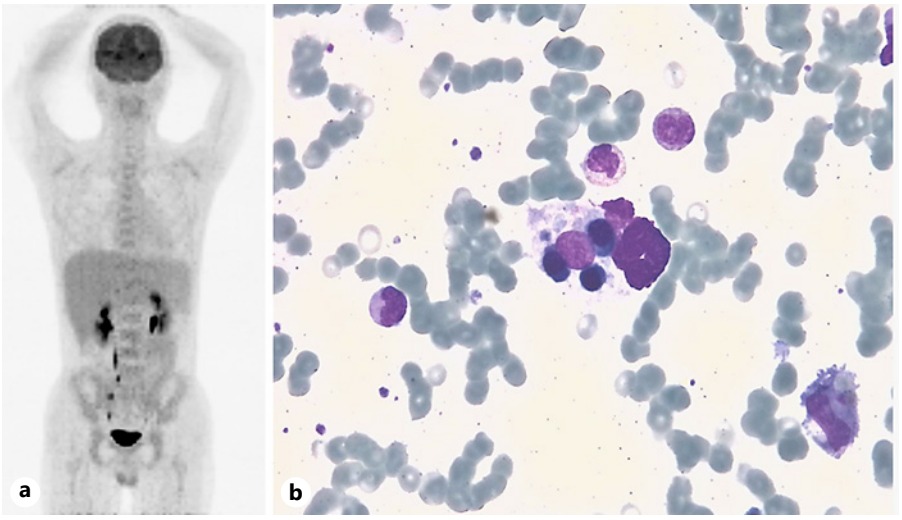

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Fig. 1. a PET-CT reveals intense FDG uptake in the bone marrow, and an increased uptake, but to a lesser extent, in the liver. The spleen did not exhibit FDG uptake. PET-CT can be a valuable tool to exclude secondary causes of HLH and identify sites of hemophagocytosis. **b** Bone marrow aspirates demonstrating evidence of hemophagocytosis (×400).

Case Report

A 21-year-old man was transferred from another hospital with an uncontrolled high fever (above 39°C), profound pancytopenia, and an elevated total bilirubin concentration (10.27 mg/dL). He experienced general weakness, a fever, myalgia, and a skin rash without an itching sensation. The patient had no known or related medical history and was in good physical condition before receiving the second dose of the BNT162b2 vaccine 2 weeks ago. He was started on empirical intravenous antibiotics (Tazoperan™, piperacillin and tazobactam, 4.5 g, q8h) for fever of unknown origin and steroid pulse therapy (intravenous methylprednisolone, 1.5 mg/kg/day) 4 days before the transfer.

Physical examination revealed an erythematous rash on the patient's arms and upper chest, icteric conjunctivae, and splenomegaly. No clinical features of thrombosis were observed. Computed tomography (CT) of the patient's neck, chest, and abdomen/pelvis demonstrated hepatosplenomegaly (spleen size, 13 cm) with periportal edema and gallbladder wall thickening, minimal pelvic ascites and bilateral pleural effusion, and no focus of infection. Blood and urine cultures were negative. Upon ^{18}F-fluoro-2-deoxyglucose (FDG)-positron emission tomography (PET)-CT, liver uptake was relatively even (standardized uptake value max/mean, 3.2/2.3), and FDG activity was not increased in the spleen (shown in Fig. 1a). A bone marrow biopsy revealed normocellular marrow with substantial histiocytosis and active hemophagocytosis, without any malignant cell infiltration (shown in Fig. 1b). A real-time polymerase chain reaction of oro- and nasopharyngeal swabs was negative for SARS-CoV-2 and other respiratory viruses. Furthermore, there was no evidence of acute or active infection with cytomegalovirus; Epstein-Barr virus; parvovirus B19; hepatitis A, B, and C; human immunodeficiency virus (HIV); or Korean endemic viruses related to hemorrhagic fever with renal syndrome. Autoimmune antibody tests, conducted to rule out the possibility of an underlying autoimmune disease, were also negative.

Overall, the patient's test results met the HLH-2004 diagnostic criteria, with an HScore of 319 (>99% probability of hemophagocytic syndrome) [15–17]. The laboratory results of the patient at presentation and the results of infection and autoimmune disorder profiles are presented in Tables 1 and 2. The patient subsequently received high-dose dexamethasone (20 mg/day for 7 days) and a 25% dose reduction on a weekly basis without etoposide or other treatment modalities. Nineteen days after steroid pulse therapy, the patient was discharged in good physical condition without any constitutional symptoms, with normal laboratory values and the disappearance of the skin rash. After discharge, the patient received oral steroids alone, which were tapered weekly, and finally stopped after the third month of follow-up without any evidence of HLH relapse.

Table 2. Patient infection and autoimmune disorder profiles

Diagnostic markers	Result
Infection markers	
SARS-CoV-2 RNA	Negative
Parvovirus B19 PCR	Negative
HIV antibody	Negative
Hepatitis A antibody IgM	Negative
HBV profile	
HBV surface antigen	Negative
HBV surface antibody	365.92 IU/L
HBV core antibody IgG	Positive
HBV core antibody IgM	Negative
HBV DNA PCR (copies/mL)	<116
Hepatitis C virus antibody	Negative
Plasma CMV DNA RT-qPCR (copies/mL)	<500
Plasma EBV DNA RT-qPCR (copies/mL)	<500
EBV early antibody IgG	Negative
EBV nuclear antibody IgG	Positive
EBV capsid antibody IgG	Positive
EBV early antibody IgM	Negative
EBV capsid antibody IgM	Negative
Hantaan virus antibody	Negative
Leptospira antibody	Negative
Orientia tsutsugamushi antibody	Negative
Autoimmune antibodies	
Anti-nuclear antibody	Negative
Anti-dsDNA antibody	Negative
Anti-Smith antibody	Negative
Rheumatoid factor	Negative
Anti-neutrophil cytoplasmic antibody	Negative
C3/C4	Normal/normal
CH50	Normal
Lymphocyte subset	
T (CD3) % (normal range, 61–85)	91.3
T4 (CD4) % (normal range, 28–58)	16.6
T8 (CD8) % (normal range, 19–48)	74.8
B (CD19) % (normal range, 7–23)	4.6
NK (CD3-CD56+CD16+) % (normal range, 61–85)	3.7
NKT (CD3+CD56+) %	0.7

CMV, cytomegalovirus; dsDNA, double-stranded DNA; EBV, Epstein-Barr virus; HBV, hepatitis B virus; NK, natural killer; NKT, natural killer T; RT-qPCR, reverse transcriptase quantitative polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Discussion

HLH is a rare disorder characterized by an overwhelming systemic inflammatory reaction. The aberrant activation of macrophages, natural killer cells, and cytotoxic T cells leads to the overproduction of cytokines, especially interleukin (IL)-1, IL-2, IL-6, and tumor necrosis factor-alpha, as well as hemophagocytosis of hematopoietic cells in the bone marrow. The resulting tissue/organ destruction means that the disease is life-threatening. Multisystem inflammatory syndrome in children (MIS-C), also a disorder caused by the dysregulated immune system, is associated with SARS-CoV-2 infection [18]. MIS-C is similar to HLH in increased T-cell activation and plasma cytokines/chemokines, but differs in the extent of the stimulation. Patients with MIS-C usually present with cardiac problems including myocarditis and often involve gastrointestinal disorders. Patients with HLH experience an unremitting high fever, cytopenia, coagulopathy, hepatic dysfunction, and organomegaly, with or without lymphadenopathies. If not treated appropriately, the patient's condition may rapidly deteriorate to terminal multiorgan failure and subsequent death [16]. Therefore, early diagnosis and urgent treatment are critical for survival [15]. HLH can be classified as either familial,

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Table 3. Clinical characteristics and treatment outcomes of patients with HLH after SARS-CoV-2 vaccination

No.	Case 1 [6]	Case 2 [7]	Case 3 [8]	Case 4 [9]	Case 5 [9]	Case 6 [10]	Case 7 [10]	Case 8 [10]	Case 9 [11]
Age/sex	68/M	43/F	36/F	20/M	71/F	60s/M	70s/F	30s/M	85/M
Underlying	Hypertension Gout Bowen's disease	EBV 824 copies/mL in plasma[a]	None	None	Hypertension	Type 2 DM	ET Breast cancer in remission	Ankylosing spondylitis	None
Vaccine[a]	ChAdOx1 nCov-19	Inactivated SARS-CoV-2	ChAdOx1 nCov-19	BNT162b2	ChAdOx1 nCov-19	ChAdOx1 nCov-19	ChAdOx1 nCov-19	ChAdOx1 nCov-19	BNT162b2
Symptom onset	10 days after 1st vaccination	Shortly after 1st vaccination	9 days after 1st vaccination	2 days after 1st vaccination	7 days after 1st vaccination	5 days after 1st vaccination	7 days after 1st vaccination	8 days after 1st vaccination	Shortly after 1st vaccination
Organomegaly[b]	Splenomegaly and LAPs	No	Hepatosplenomegaly	Splenomegaly and LAPs	Splenomegaly and LAPs	Hepatomegaly	No	Splenomegaly	No
Neutrophils, 10^9/L	N/A	0.70	31.20	0.72	0.32	N/A	N/A	N/A	9.2
Hemoglobin, g/dL	N/A	11.3	11.5	13.2	14.6	10.1	11.9	10.5	Normal
Platelets, 10^9/L	59	27	243	86	26	54	69	319	34
Ferritin, µg/L	11,801	8,140	12,423	6,592	>16,500	159,076	5,529	58,255	378
Triglycerides	2.3 mmol/L	2.4 mmol/L	1.8 mmol/L	5.9 mmol/L	27.8 mmol/L	6.3 mmol/L	2.0 mmol/L	2.7 mmol/L	2.7 mmol/L
Fibrinogen	2.3 g/L	1.4 g/L	5.5 g/L	9.9 g/L	9.3 g/L	0.7 g/L	0.9 g/L	4.2 g/L	4.3 g/L
BM hemophagocytosis	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	Yes
Soluble CD25[c]	733 U/mL	204.99 pg/mL	N/A	2,806 U/mL	2,703 U/mL	4,833 pg/mL	9,232 pg/mL	3,575 pg/mL	N/A
NK cell activity	Normal	Decreased	N/A	Decreased	Normal	N/A	N/A	N/A	N/A
HScore	250	261	N/A	229	293	259	220	219	N/A
Other complications	No	No	No	No	DVT	Bilateral pleural effusions Multiorgan failure	Acute pneumonitis	LV dysfunction	N/A
Treatment	Not treated	Dexamethasone	Methylprednisolone + IVGV	Dexamethasone	Dexamethasone + etoposide	Methylprednisolone + IVGV + anakinra	Methylprednisolone + IVGV + anakinra	Methylprednisolone	N/A
Outcomes	Alive	Alive	Alive	Alive	Alive	Alive	Died[d]	Alive	N/A

Table 3 (continued)

No.	Case 10 [12]	Case 11 [12]	Case 12 [12]	Case 13 [12]	Case 14 [12]	Case 15 [13]	Case 16 [14]	Case 17 (our case)
Age/sex	52/M	53/M	57/M	55/F	48/F	38/F	24/F	21/M
Underlying	T-cell lymphoma	ILD	Controlled HIV	MDS, MAC, aspergillosis	HIV/AIDS MAC-IRIS	None	None	None
Vaccine[a]	BNT162b2	BNT162b2	mRNA-1273	BNT162b2	mRNA-1273	BNT162b2	BNT162b2	BNT162b2
Symptom onset	1 day after 1st vaccination	4 days after 1st vaccination	12 days after 1st vaccination	3 days after 1st vaccination	8 days after 1st vaccination	21 days after 2nd vaccination	10 days after 1st vaccination	14 days after 2nd vaccination
Organomegaly[b]	Splenomegaly	Hepatomegaly	No	Hepatosplenomegaly	No	N/A	Splenomegaly	Splenomegaly
Neutrophils, 10^9/L	WBC count, 5.4	WBC count, 3.0	WBC count, 4.7	WBC count, 2.6	WBC count, 10.6	0.9	WBC count, 1.95	0.35
Hemoglobin, g/dL	11.1	11.5	8.4	6.8	12.1	9.8	Anemia	9.6
Platelets, 10^9/L	172	21	9	106	310	N/A	Thrombocytosis	37
Ferritin, µg/L	8,130	75,249	>15,000	7,724	285	500	138	23,639
Triglycerides	650 mg/dL	263 mg/dL	142 mg/dL	106 mg/dL	138 mg/dL	225 mg/dL	Elevated	32.4 mmol/L
Fibrinogen	105 mg/dL	435 mg/dL	<35 mg/dL	561 mg/dL	527 mg/dL	normal	Elevated	1.3 g/L
BM hemophagocytosis	Yes	Yes	N/A	N/A	N/A	Yes	No	Yes
Soluble CD25[c]	25,603 pg/mL	18,100 pg/mL	2,473 pg/mL	4,907 pg/mL	N/A	2,610 U/mL	N/A	5,776 U/mL
NK cell activity	N/A	N/A	N/A	N/A	N/A	Decreased	N/A	Decreased
HScore	239	213	185	208	130	147	259	319
Other complications	*Bacteroides* bacteremia	ILD aggravation	Respiratory failure	No	Relapsing pulmonary IRIS flares	No	No	Skin rash
Treatment	Dexamethasone + etoposide	Dexamethasone + IVGV + anakinra	Methylprednisolone	Anakinra	Prednisone + Infliximab	Methylprednisolone	Dexamethasone + IVGV + anakinra	Methylprednisolone → Dexamethasone
Outcomes	Died	Alive	Died	Alive	Alive	Alive	Alive	Alive

BM, bone marrow; COVID-19, coronavirus disease 2019; DM, diabetes mellitus; DVT, deep vein thrombosis; EBV, Epstein-Barr virus; ET, essential thrombocythemia; HIV, human immunodeficiency virus; ILD, interstitial lung disease; IRIS, immune reconstitution inflammatory syndrome; IVGV, intravenous immunoglobulin; LAPs, lymphadenopathies; LV, left ventricle; MAC, *Mycobacterium avium* complex; MDS, myelodysplastic syndrome; mRNA, messenger RNA; NK, natural killer; PTE, pulmonary thromboembolism; WBC, white blood cell; SARS-COV-2, severe acute respiratory syndrome coronavirus 2. [a] All patients had negative COVID-19 serology test results. The patient's EBV serology profile (EB-VCA IgA negative, EB-VCA IgM negative, EB-VCA IgG positive, EB-VEA IgA negative, EB-VEA IgG negative, and EB-VNA IgG positive) showed that the EBV infection was not a recent event. [b] All patients with LAPs underwent lymph node biopsy to exclude malignancy. [c] The reports used different units and reference ranges of soluble CD25. The soluble CD25 reference ranges were 27–118 U/mL and 0–2,500 pg/mL. [d] This patient developed atrial fibrillation with hemodynamic compromise and spontaneous pneumothorax and was moved to the intensive care unit for vasopressors, continuous veno-venous hemofiltration, and chest drains. However, the patient died because of spontaneous rupture of the esophagus. The reports used different units and reference ranges of soluble CD25. The soluble CD25 reference ranges were 27–118 U/mL and 0–2,500 pg/mL.

characterized by genetic defects causing lymphocyte cytotoxicity (mutations of various genes, such as *PRF1*, *STX11*, *UNC13D*, or *STXBP2*) [19], or acquired/secondary HLH (sHLH), usually triggered by infection, autoimmune disease, or malignancy [20–22]. In particular, it is critical to exclude malignancy-associated HLH due to lymphomas including intravenous B-cell lymphoma and aggressive T-cell lymphoma in Asian populations, considering the high prevalence and similar clinical features [22]. The diagnosis of HLH is commonly based on the criteria of the HLH-2004 study, which were developed using pediatric patient data; it has not been validated in adults [15]. An alternative is the HScore, a diagnostic scoring system for HLH developed based on clinical parameters of the adult population [17]. In this case, the patient met the criteria for both measures: he fulfilled all eight of the HLH-2004 diagnostic criteria and had an HScore of 319. There was no clear precipitant of HLH other than the second dose of the BNT162b2 vaccine. The patient had no remarkable medical history, was not taking any medications, and had no active or recent bacterial or viral infection or autoimmune disease. After his diagnosis, the patient recovered entirely without relapse or sequelae with the administration of dexamethasone steroid pulse therapy with slow tapering; the HLH-94 treatment protocol was not strictly followed [20]. The HLH-94 protocol was initially designed for pediatric patients; it includes administering steroids, etoposide, cyclosporin, and immunoglobulins. The schedule and dosage should be modified for adults to avoid severe complications related to comorbidities or multiorgan damage caused by cytokine storms [16].

sHLH was previously reported in patients who had a SARS-CoV-2 infection. Furthermore, as sHLH is similar to hyperinflammatory syndrome, it may be underdiagnosed in severe cases of COVID-19 [23]. Administration of the IL-1 inhibitor, anakinra, and the IL-6 inhibitor, tocilizumab, showed improvements in patients hospitalized with COVID-19-induced sHLH and severe COVID-19, respectively [24, 25]. Recent studies also suggest that the anti-interferon gamma antibody, emapalumab, and the JAK1/2 inhibitor, ruxolitinib, are available treatment options for sHLH [16, 26, 27]. Although the mechanisms of COVID-19 vaccination-related sHLH remain unknown, overwhelming immune stimulation by mRNA- or DNA-based vaccines may trigger a massive cytokine storm, which may result in sHLH. We are aware of 17 cases of SARS-CoV-2 vaccination-related sHLH to date, including our case (Table 3) [6–14]. All of these cases fulfilled the diagnostic criteria of either HLH-2004 or the HScore after receiving the BNT162b2 (n = 8), ChAdOx1 nCov-19 (n = 6), mRNA-1273 (n = 2), and inactivated SARS-CoV-2 (n = 1) vaccinations. Secondary causes of HLH were excluded by extensive infection screening and autoimmune panels. Most of the patients with COVID-19 vaccination-related sHLH experienced symptomatic onset at a median of 7.0 (range, 0–21) days, and 15 of 17 were after the first dose. Therefore, physicians should be aware that, although rare, sHLH is a potentially catastrophic complication of any currently available COVID-19 vaccine, after either the first or second dose. We suggest that patients be closely monitored for any constitutional symptoms or laboratory abnormalities after vaccination for at least 3 weeks.

In one of the 17 patients, sHLH completely resolved without any treatment (case 1) [6]. For another patient, treatment and clinical outcomes were not reported (case 9) [11]. The other patients received steroid pulse therapy (n = 15), in some cases combined with either etoposide (n = 2) or another second-line therapy, such as anakinra (n = 5) or infliximab (n = 1), and/or immunoglobulin infusion (n = 5); the steroids were gradually tapered, and there was no relapse of sHLH. Although we did not utilize second-line therapy in our case, anakinra reportedly has a tolerable safety profile and acceptable clinical outcomes in patients with sHLH related to COVID-19 infection or vaccination [10, 12, 14, 23]. Therefore, we suggest utilizing corticosteroids as the treatment backbone and adding anakinra in severe cases, in which sHLH cannot be controlled solely with corticosteroids. Three of the patients died, all with substantial comorbidities (case 7, breast cancer and essential thrombocythemia; case 10, lymphoma; and case 12, HIV infection) [10, 12].

This case report should not be used as support to avoid vaccination, as the vaccine remains an essential and promising tool to overcome the COVID-19 pandemic. We believe that early recognition and initiation of corticosteroids, combined with anakinra in severe cases, are critical to prevent irreversible organ damage and death. Therefore, vaccinated patients should be carefully monitored for signs and symptoms of HLH.

Statement of Ethics

This case report was approved by the Institutional Review Board and Ethics Committee of the Catholic Medical Center, Republic of Korea (KC22ZASE0149), and was conducted in accordance with the tenets of the Helsinki Declaration. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Hee Won Park and Gi June Min were the treating physicians and participated in the study design and writing of the manuscript. Tong Yoon Kim and Seok-Goo Cho contributed to the writing of the manuscript and discussion of the case with the literature review. Seok-Goo Cho reviewed the manuscript. Gi June Min participated in the pathological analyses and discussion of the study design. All authors have read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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